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EXAMINER	
BORIN, MICHAEL L	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/730,214	MILLER ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *22-26,28,29,31-33 and 35-40* is/are pending in the application.

4a) Of the above claim(s) *30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26,28,29,31-33 and 35-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/11/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/11/2004 has been entered.

Status of Claims

2. Claim 34 is canceled. Claims 22-26, 28,29,31-33, 35-40 are pending.

Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application

As was stated in the previous Office actions, in view of plurality of issues addressed in rejections under 35 U.S.C. 112, first and second paragraphs, as well as under 35 U.S.C. 101, it was deemed necessary to resolve these issues prior to applying appropriate art rejections. The remaining rejections are supplemented by new rejections under the same statutes.

Amended claim 30, which is now an independent claim, is directed to an invention that is independent or distinct from the invention of claims 22-26, 28,29, 31-33, 35-40 for the following reasons: The inventions are drawn to methods that have different modes of operation: the invention of claims claims 22-26, 28,29, 31-33, 35-40 is based on designing proteins based on determining hydrophobicity, whereas the invention of claim 22 is based on designing proteins based on determining Variance. Since applicant has received actions on the merits for the the claims drawn to method for designing proteins based on determining hydrophobicity, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 30 is withdrawn from consideration as being directed to a non-elected invention.

Information Disclosure Statement

3. Applicants' Information Disclosure Statement filed 08/11/2004has been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Claim Rejections - 35 U.S.C. § 101 (non-statutory invention)

4. Claims 22-26, 28,29,31-33, 35-40 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The instant claims, as amended, are drawn to computation or manipulation of data or abstract information and as such is non-statutory subject matter due to being drawn to a non-tangible mathematical invention. No production or change in actual material is seen in the instant claims as amended and thus it is deemed non-statutory subject matter.

Claim Rejections - 35 USC § 112, first paragraph (written description)

5. Claims 22-26, 28,29,31-33, 35-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the

claimed invention. Claim 22 introduces new matter as it recites the following terms (underlined):

- configurations of fixed length
- ...or another space filling generic side chain
- ...another space-filling generic side chain
- ...evaluating the surface exposure ...of generic side chain

There is no disclosure in the specification on the meaning and scope of the definition of the recited terms and there is no guidance on how to practice the claimed method with such embodiments (see below).

Claim Rejections - 35 USC § 112, second paragraph.

6. Claims 22-26,28,29,31-33,35-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

A. Claim 22,second step: The newly applied term "fixed radius" in regard to "a sphere" is not clear. Specification, p. 8, lines 15-19, guides that in order to arrive to the size of the radius one is expected to select " a representative set of

"natural backbone configuration" and then the "radius ... is the largest radius for which the natural backbone configurations are not self-intersecting". Neither the term "natural backbone configuration" (What is "natural configuration" for a backbone? "Natural" in terms of origin, environment, 3-D orientation?) , nor criteria for selecting the "natural backbone configuration" are offered in the disclosure. It is not clear which one out of plethora of natural protein configurations is to be selected and how it is supposed to be applied to the designed model backbone configuration?

B. Claim 22, second step: The newly applied term "another space-filling generic side chain" used as an alternative to use of spheres of "fixed radius" is also vague and indefinite. The term is a new matter introduced in the latest version of the claims; there is no guidance on what constitutes "a space-filling generic side chain", what 3-D structure it has (which is essential for subsequent calculations), how it is to be applied to the designed backbone configuration, and how subsequent method steps are to be performed for a backbone decorated with with " space-filling generic side chains".

C. Claim 22, step four: it is not clear how to evaluate "surface exposure of generic side chain".

D. Claim 22, step 6: the term "generating sequence of hydrophobicities" is not clear. The preceding method steps deal with protein backbone populated with "spheres" or "space-filling generic side chains" that represent potential space that might be occupied by an amino acid, but are not related to any physico-chemical properties of particular amino acid residue, such as hydrophobicity. Specification, p. 9, lines 24-25, guides that "each sequence is reduced to the pattern of hydrophobicities of its individual amino acids". However, there are no "individual amino acids" in the protein backbone populated with "spheres" or "space-filling generic side chains" .

Even more unclear is the next guidance of specification (p. 9, lines 30-31) instructing that "set of hydrophobicities" is to be "randomly generated". Does it mean that the sequences of hydrophobicities" recited in the claim is completely random and unrelated to any preceding step?

Further, the same sentence of specification requires the randomly generated set of sequences of hydrophobicities to be generated "with uniform weight on the space of the allowed sequences". The term "allowed sequences" is not clear and is not defined. At which point sequences become "allowed" and which sequences are meant – sequences of model amino acid residues, sequences of hydrophobicities? And how "uniform weight" of the "allowed sequences" is being determined? It is noted that in previous communication applicant explained that the term "uniform weight" refers to "spacing between amino acids" and directed

examiner's attention to p. 9, lines 23-32 of specification. However, Examiner failed to allocate there any such explanation of the term.

E. Claim 22, step 7: The step is directed to determining ground state, or the state with the lowest energy, for a sequence of hydrophobicities. The determination is based on formula (1), page 10, which includes hydrophobicity if each element of the sequence. As was discussed again, the first five steps of the method deal with a modeled peptide backbone populated with "spheres" or "space-filling generic side chains" that represent potential space that might be occupied by an amino acid, but are not related to any physico-chemical properties of particular amino acid residue, such as hydrophobicity. Hence, it remains unclear how a ground state for sequences of "real" amino acid residues can be calculated.

F. Claim 22, step 8: This method step requires recording of ground state for each sequence (emphasis added). To the contrary, specification guides that "it is not necessary to find the ground-state configuration for all sequences". see p. 10, lines 14-15. Then it is not clear whether calculartion of all (as claimed) or some (as disclosed in specification) ground-state configurations is required in the method.

Claim Rejections - 35 USC § 112, first paragraph (enablement).

7. Claims 22-26, 28,29,31-33, 35-40 are rejected under 35 U.S.C. 112, first paragraph, as based on specification which is not enabling. The rejection is applied for the following reasons:

A. Claim 22, first step: The method is based on generating configurations of "fixed length". The term "of fixed length" is a new matter, it is not defined in the specification, and it is not clear backbones of what "fixed length" are within the scope of the invention.

B. Claim 22, second step: This step of claim 22 requires use of spheres of "fixed radius". The selection of the "fixed radius" is not clear: in order to arrive to the size of the radius one is expected to select " a representative set of "natural backbone configuration" and then the "radius ... is the largest radius for which the natural backbone configurations are not self-intersecting". See p. 8, lines 15-19. Neither the term "natural backbone configuration" (What is "natural configuration" for a backbone? "Natural" in terms of origin, environment, 3-D orientation?) , nor criteria for selecting the "natural backbone configuration" are offered in the disclosure . It is not clear which one out of plethora of natural protein configurations is to be selected and how it is supposed to be applied to the designed model backbone configuration? Consequently, an artisan would not be appraized of the scope of the invention and would not be able to make the invention as claimed.

C. Claim 22, second step: As an alternative to use of spheres of "fixed radius" this step of claim 22 suggests use of "another space-filling generic side chain". The term is a new matter introduced in the latest version of the claims; there is no

guidance on what constitutes "a space-filling generic side chain", what 3-D structure it has (which is essential for subsequent calculations), how it is to be applied to the designed backbone configuration, and how subsequent method steps are to be performed for a backbone decorated with with " space-filling generic side chains". ? Consequently, an artisan would not be appraised of the scope of the invention and would not be able to make the invention as claimed.

D. Claim 22, step four: it is not clear how to evaluate "surface exposure of generic side chain", consequently, it is not clear how to make the invention as claimed.

E. Claim 22, step 6: the term "generating sequence of hydrophobicities" is not clear. The preceding method steps deal with protein backbone populated with "spheres" or "space-filling generic side chains" that represent potential space that might be occupied by an amino acid, but are not related to any physico-chemical properties of particular amino acid residue, such as hydrophobicity. Specification, p. 9, lines 24-25, guides that "each sequence is reduced to the pattern of hydrophobicities of its individual amino acids". However, there are no "individual amino acids" in the protein backbone populated with "spheres" or "space-filling generic side chains." Note that applicant argues (response of 08/11/2004, paragraph bridging pages 16 and 17, that "it is not necessary to select specific

amino acids in the early steps of the design process. By assigning of generic spheres to the position that amino acid residues would occupy, one would be able to implement the subsequent method steps...". Examiner disagrees: given lack of guidance on how to correspond modeled "populated backbone" to a natural protein sequences, it is not clear how to get from early method steps of designing the modeled backbone to "sequences of hydrophobicities".

Even more unclear is the next guidance of specification (p. 9, lines 30-31) instructing that "set of hydrophobicities" is to be "randomly generated". Does it mean that the sequences of hydrophobicities" recited in the claim is completely random and unrelated to any preceding step? And what this step has to do with the preceding steps?

Further, the same sentence of specification requires the randomly generated set of sequences of hydrophobicities to be generated "with uniform weight on the space of the allowed sequences". The term "allowed sequences" is not clear and is not defined. At which point sequences become "allowed" and which sequences are meant – sequences of model amino acid residues, sequences of hydrophobicities? And how "uniform weight af the allowed sequences" is being determined?

Without said information, it is not clear how to make the invention as claimed.

Claim Rejections - 35 U.S.C. § 101 (utility)/ 112-1

8. Claims 22-26, 28,29,31-33, 35-40 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by a substantial utility or a well established utility.

The invention is drawn to method for designing proteins by a computative method which designs a protein backbone populated with model spheres or space-filling generic side chains, generating sequences of randomly generated hydrophobicities, and identifying highly designable configurations. The claims do not recite any steps of preparing particular proteins of interest, are not directed to determining designability of proteins related to any natural proteins of interest. An *in silico* method to design proteins for a particular activity would have a patentable utility. However, as set forth above, the instant claims do not recite design of any particular protein.

The Court of Customs and Patent Appeals has stated:
"Practical utility is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public."

A "use" to do further research is not considered a utility which provides an "immediate benefit" to the public.

Examples of situations requiring further research to identify or reasonably confirm a "real world" context of use, and which do not have utility under 35 USC 101, as set forth in MPEP 2107.01.1, include:

(A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved',
and
(C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility.

Applicant argues that "the utility of the claimed invention is as a means of applying the powerful computational tools available today to test myriad combinations of backbone configurations and amino acid sequences and to thereby determine novel structures that have potential "real world" application." (p. 17 of the response). Examiner agrees that the method produces some amino acid sequences, but disagrees in regard to immediately recognizable "real world" use of these arbitrary sequences. This is because the method is not directed to any particular protein of interest, but rather is aimed at modeling protein backbone populated with model spheres or space-filling generic side chains and generating sequences of randomly generated hydrophobicities for which low energy state configuration in being determined. There is no indication that proteins produced by such method have any utility (e.g., have any pharmaceutical utility). Furthermore, there are no specific examples of the claimed design method present in the specification that would attest to any utility of the method. Examiner maintains that the specification does not relate to any "real world" substantial utility of the claimed method and that further research is needed to identify the immediate benefit to the public from using the method. In this regard Examiner maintains that the reference of Shakhnovitch et al is relevant:

> "Most of the present experimental [protein design] approaches enjoyed only limited success, providing polypeptides that in most cases fold into compact but mostly disordered conformations of molten-globule-like species. It is quite possible that limitations in experimental design result from a relatively low ynergism between experiment and theory."
>
> p. R45, right column.

Identifying use of the claimed method of polypeptide design would require carrying out further research. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Consequently, the claimed subject matter is not supported by substantial or well established utility.

9. Claims 22-26, 28,29,31-33, 35-40 are also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Conclusion.

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

10/22/04